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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Use of double-blind placebo-controlled N-of-1 trials among stimulant-treated youths in The Netherlands: a descriptive study

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Abstract
Objectives An N-of-1 trial is a double-blind placebo-controlled randomized trial to objectively and systematically evaluate the individual's response. This approach seems extraordinarily suitable for assessing the efficacy of stimulants in the treatment of attention deficit hyperactivity disorder (ADHD). The aim is to examine the use of N-of-1 trials among youths in the Netherlands, the protocols used, and the continuation of stimulant treatment thereafter.
Methods Physicians requesting N-of-1 trials with stimulants were interviewed about their rationale and protocol. Prevalence and continuation were investigated by extracting N-of-1 trials among youths <20 years of age from a large pharmacy dispensing database for 2000–2004.
Results The main purpose of N-of-1 trials mentioned by physicians was the assessing of individuals' response and dose-finding. Trial length, dosing schedule and efficacy assessment differed per physician. Trials consisted of a maximum of two treatment periods per dose. The annual percentage of youths starting stimulant treatment with an N-of-1 trial fluctuated between 0.6% (3/462) and 3.3% (10/301). No statistical significant difference could be detected between the continuation of stimulant treatment with or without an N-of-1 trial (p=0.71).
Conclusions N-of-1 trials with stimulants are infrequently and not optimally used in the Netherlands. The results of N-of-1 protocols described by physicians are of questionable value, due to the small number of treatment periods per dose. More uniformity in the protocols would make it easier to encompass the N-of-1 methodology in physicians' daily practice.

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Introduction

In many Western countries, the use of stimulants among youths has increased markedly in the last decade [16, 19, 21, 29]. Stimulants are the first-choice medication in the treatment of attention deficit hyperactivity disorder (ADHD). In 70–80% of the youths, stimulants reduce hyperactivity, impulsiveness and inattentiveness [2]. ADHD was once thought to disappear as children grew up, but follow-up studies in youths with ADHD have shown considerable persistence of the disorder into adulthood [5, 3]. For these patients, long-term treatment with stimulants may be indicated. The impact of long-term stimulant use, however, is still unclear [10].

As up to 30% of youths will not respond to stimulant treatment [2], it is important to evaluate the effect of stimulant treatment in the individual child at an early stage of treatment. A useful method that helps the physician and family to evaluate the effect of medication in individuals is the N-of-1 or single-subject trial [4, 8]. An N-of-1 trial is a double-blind placebo-controlled randomized trial to objectively and systematically assess individual response. In an N-of-1 trial, a single patient undergoes a series of crossovers with active treatment/placebo, high dose/low dose or first choice/alternative treatment. The order of administration is determined by random allocation and the patient and physician are blinded for the treatment order. Target symptoms are assessed and interpreted afterwards. The N-of-1 methodology is not suitable for all disorders and pharmacological treatments. Apart from the benefit-risk balance of the treatment being in doubt, the disorder should be chronic and relatively stable. Furthermore, treatment must have a rapid onset and termination of action, ruling out carry-over effect into the next treatment period.

An N-of-1 trial seems ideal for evaluating the efficacy of the stimulant methylphenidate in youths diagnosed with ADHD. First, ADHD is nowadays considered a chronic disorder, showing rather consistent symptoms. Second, methylphenidate has a rapid onset (.5–1 h) and termination of action (4–6 h) [23]. Furthermore, rational evaluation of behaviour is hard, and the placebo-controlled double-blind design enables a more objective evaluation of behavioural changes due to medication [4].

Several papers on stimulant treatment making use of the N-of-1 methodology have been published. The methodology was used for dose-finding and evaluation of side effects in several clinical trials on stimulant treatment in youths with ADHD [1, 18, 24]; however, in these papers, the N-of-1 methodology received no further attention. Parental acceptance, satisfaction and compliance of methylphenidate treatment after an N-of-1 trial were investigated by Johnston and Fine [11]. Other studies illustrated how N-of-1 trials with methylphenidate can be used in routine clinical practice [6, 14, 17] and Kent et al. promoted the technique as practical, useful and highly endorsed by families [13]. Furthermore, in the literature, several suggestions have been proposed to enhance reliable and unbiased interpretation of the effect of medication such as assigning consistent raters, tailoring the outcome measures, blind evaluation of trial outcome and the use of statistical tests [4, 20, 26].

Most studies on the use of N-of-1 trials in stimulant treatment in clinical practice were limited to single clinics in North America [6, 11, 13, 14]. As far as we know, no research has been done to examine the frequency of use of N-of-1 trials with stimulants in the general paediatric population. In this study, we examined the occurrence of N-of-1 trials when starting stimulant treatment in The Netherlands, and interviewed physicians about their protocols. Using this information, we derived the proportion of stimulant treatments, starting with an N-of-1 trial, and the continuation of stimulant treatment using pharmacy data.

Methods

The data sources used included physicians and a large pharmacy-dispensing database.

Physicians' interviews

To reach physicians conducting N-of-1 trials with stimulants for an interview, a brief questionnaire was sent to 102 randomly selected pharmacies. Pharmacists play an essential role in performing an N-of-1 trial because they prepare the blinded stimulant and placebo capsules. Pharmacists were asked if they had provided an N-of-1 trial with stimulants in the past year. If so, pharmacists were asked for names of physicians who had requested an N-of-1 trial. Then the physicians were called to ask to participate in an interview. The questions asked were about their considerations in using the N-of-1 method in stimulant treatment and details of the protocols used. During the interview, the physicians were given ample opportunity to provide additional information about their N-of-1 method. Information about these protocols was used to identify N-of-1 trials in the database part of the study. During the major part of the study period, short-acting methylphenidate and dexamphetamine were the available and reimbursed stimulants on the Dutch market. Long-acting methylphenidate became available without regular reimbursement at the end of 2003.

Database study

The quantitative part of this study was performed with the InterAction database (IADB), which contains prescription drug dispensing data from about 50 community pharmacies in the northern and eastern part of the Netherlands. The IADB covers all prescriptions from an estimated population of approximately 450,000 since 1999 [22, 25]. This database includes all prescriptions, regardless of prescriber, insurance, or reimbursement status, apart from over-the-counter drugs and drugs dispensed during a hospital stay. Each prescription record comprises information about the drug, date of dispensing, amount dispensed, dose regimen and the prescribing physician. All drugs are coded according to ATC-classification. Each patient has a unique, though anonymous, identifier. Due to a high patient-pharmacy commitment in the Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete [15].

From the IADB, we derived a study population of all incident stimulant users aged 0–19 years with a first-time prescription of stimulants dispensed during 2000–2004. Youths were regarded as incident users if they received a stimulant prescription, without having had any stimulant prescriptions in the preceding year, while being registered in the IADB. Data from 1999 were used to identify incident users in 2000.

Based on information on the N-of-1 protocols from the physician interviews, potential N-of-1 trials were defined as dispension of at least two prescriptions for compounded stimulant capsules and other compounded capsules to the same person from the same pharmacy within a time frame of 1 month. Medication profiles of ten selected patients from the IADB receiving a potential N-of-1 trial with stimulants were presented to four pharmacists. Within this group, consensus was quickly reached about what could be considered an N-of-1 trial at the start of stimulant treatment. Criteria were: (1) dispension of compounded methylphenidate capsules and placebo capsules with inert excipients like lactose powder or cornstarch only, (2) within a time frame of 2 weeks (3) to one person (4) from the same pharmacy. From the medication profiles of the incident stimulant users in the IADB, N-of-1 trials with methylphenidate were extracted using the criteria above. Since more than 99% of the incident stimulant users in the Netherlands receive methylphenidate [7], we only considered N-of-1 trials with methylphenidate. Of the initially 46 potential N-of-1 trials detected, 31 satisfied all four criteria. All 15 excluded cases received compounded capsules with adjunct medication besides stimulant capsules and had received no placebo capsules.

The percentage of incident users starting stimulant treatment with an N-of-1 trial per total number of incident stimulant users was estimated per year. Continuation of stimulant treatment after an N-of-1 trial was compared to other starters using Kaplan-Meier survival estimators. Stimulant treatment was considered discontinued when a youth had not received stimulant prescriptions for at least 365 consecutive days after the dispension date of the final prescription plus half the number of days of the final prescription. A log-rank test was used to test for overall differences in the continuation of therapy between starting treatment with and without an N-of-1 trial. Statistical tests were considered significant when $p<0.05$ (two-tailed).

Results

Physicians' interviews

Of 102 pharmacists to whom a questionnaire was sent, 51 responded of whom 24 pharmacists were able to mention names of 14 physicians requesting an N-of-1 trial in the past year. The 9 remaining pharmacists were unwilling or unable to give a name (e.g. only institute name available or physician moved office). Fourteen physicians were approached for an interview. One child psychiatrist and one paediatrician were not willing to participate due to busy schedules. The remaining 12 physicians were interviewed; 7 child psychiatrists, 1 adult psychiatrist, 2 paediatricians, 1 youth health care physician and one family doctor.

Eight physicians (8/12 or 67%) perceived the N-of-1 methodology as a customary procedure when stimulant treatment was considered (Table 1). One physician also used the method to evaluate continuation of stimulant treatment. The main purpose for conducting an N-of-1 trial was assessing individuals' response to stimulants and examining the optimal dose for most of the interviewed physicians. All physicians used a double-blind placebo-controlled trial in which the pharmacist was responsible for the randomization and for preparing the blinded methylphenidate and placebo capsules. Treatment periods were applied in random order. No protocol was the same, as trial length, dosing schedule, frequency of rating outcome and number of crossover periods differed per protocol. According to most protocols the parents and teacher of the child assessed target symptoms during the trial, and scores were visually evaluated afterwards. The abbreviated Conners' parent and teacher rating scales were used for measuring outcome by 8 of 12 physicians (67%). Adverse effects were assessed and evaluated in 3 of the 12 protocols (25%).

Database study

Using the pharmacy database IADB, a total of 1,769 youths starting treatment with stimulants in the period 2000–2004 were detected. The median age was 9 years and the male-to-female ratio among these starters was 3.4:1. The percentage starting treatment with an N-of-1 trial with methylphenidate fluctuated between 0.6% (3/462) and 3.3% (10/301) per year during 2000–2004 (Table 2). The median age in youths starting stimulant treatment with an N-of-1 trial was not statistically different from other starters (for both groups 9.0 years, $p=0.84$). The male-to-female ratio among youths starting stimulant treatment with an N-of-1 trial was 4.2:1 and did not significantly differ statistically from the male-to-female ratio in other starters (3.4:1, $p=0.64$). After 5 weeks, the cumulative probability of continuation of stimulant treatment was 0.89 (95%CI 0.77–1.0) among youths starting with an N-of-1 trial and 0.89 (95%CI 0.87–0.91) for other starters (Fig. 1). Also, no overall statistically significant difference could be detected between continuation of stimulant treatment in youths starting with an N-of-1 trial and the other starters ($p=0.71$, 1df).

Table 1 Questions and answers of interviews with physicians (n=12) conducting N-of-1 trials with methylphenidate

	No. physicians
When do you offer an N-of-1 trial?	
Customary procedure if stimulant treatment is considered	8
If stimulant treatment is considered, but not as a customary procedure	3
Customary procedure if stimulant treatment is considered and for evaluation of treatment	1
For what purpose do you use an N-of-1 trial with stimulants?	
Assessing effectiveness and optimal dose methylphenidate	8
Assessing effectiveness	3
To convince parents who are reluctant to stimulant treatment	1
Which dosing schedule do you apply?	
4 periods of 1 week, comparing placebo and 3 different doses methylphenidate	5
4 periods of 1 week, comparing placebo and 2 different doses methylphenidate	4
4 periods of 1 week, comparing placebo and 1 dose of methylphenidate	1
2 periods of 1 week, comparing placebo and 1 dose methylphenidate	1
4 periods of 2 weeks, comparing placebo and 1 dose methylphenidate	1
What is the frequency of dosing during a trial day?	
2× per day	11
2 or 3× per day	1
How are target symptoms assessed during the trial? Use of	
Abbreviated Conners' rating scale	8
Score list (self-made)	2
DSM IV[a] criteria	1
Diary	1
How often are target symptoms assessed during the trial?	
Daily	6
Weekly	5
Minimal (at least on 2 weekdays and during the weekend)	1
Do you use an adverse effects questionnaire?	
No	9
Yes	3
Do you use statistical tests to interpret the outcome of the trial?	
No	12

[a] Diagnostic and Statistical Manual of Mental Disorders, 4th edition

Table 2 Prevalence of starting stimulant treatment in youths <20 years with an N-of-1 trial in the period 2000 to 2004

Year	No. of starters	No. starting with N-of-1 trial	% starting with N-of-1 trial	95% CI
2000	313	6	1.9	0.7–4.1
2001	301	10	3.3	1.6–6.0
2002	313	3	1.0	0.2–2.8
2003	380	9	2.4	1.1–4.4
2004	462	3	0.6	0.1–1.9

Discussion

Two thirds of the responding Dutch pharmacists had provided an N-of-1 trial with stimulants in the last year. Usually, requests came from child psychiatrists or paediatricians who used the N-of-1 methodology for determining individuals' response and dose-finding, and each of these physicians used his or her own protocol.

Similar to other studies, we found that assessing individuals' response and dose-finding were the main reasons for physicians to apply an N-of-1 trial [11, 13, 14]. Other reasons mentioned in the literature were discouraging both overenthusiastic prescribing and a priori rejection of stimulant therapy [14] and positively influencing parents' views regarding the acceptability of methylphenidate [11]. The latter was reported by one physician in our study who performed an N-of-1 trial only in case parents were reluctant to stimulant treatment.

Although none of the Dutch physicians followed the same N-of-1 procedure exactly, most of the N-of-1 procedures were roughly similar to the ones used in two outpatient clinics in Canada [11, 13, 14]. Mostly placebo and methylphenidate treatment periods of 1 week were used, different methylphenidate doses were compared and Conners' rating scales were used to measure effectiveness. However, trial length was 3 weeks in the Canadian centres, while 4 weeks was most commonly found in our study. In two other North American studies among institutionalized youths with ADHD, placebo and methylphenidate treatment periods were shorter, as randomization took place per day or per 4 days, resulting in a trial length of 6–16 days [14, 26]. Probably in our community setting and in the Canadian outpatient clinics, treatment periods of 1 week were chosen because shorter treatment periods were difficult to implement in an outpatient setting.

The frequency of measuring outcome during an N-of-1 trial varied between daily to weekly ratings in our study, a variation also found in the literature [11, 13, 14, 26]. We prefer daily outcome measurements, because in that way, day-to-day variation in ADHD symptoms and treatment effect (caused by multiple factors) is represented, something that is ignored when rating only once a week. After all, it may be hard to give a well-considered overall judgment of behaviour at the end of a treatment period of 7 days.

It is of concern that all physicians evaluated the trial outcome measurements by visual inspection and not by

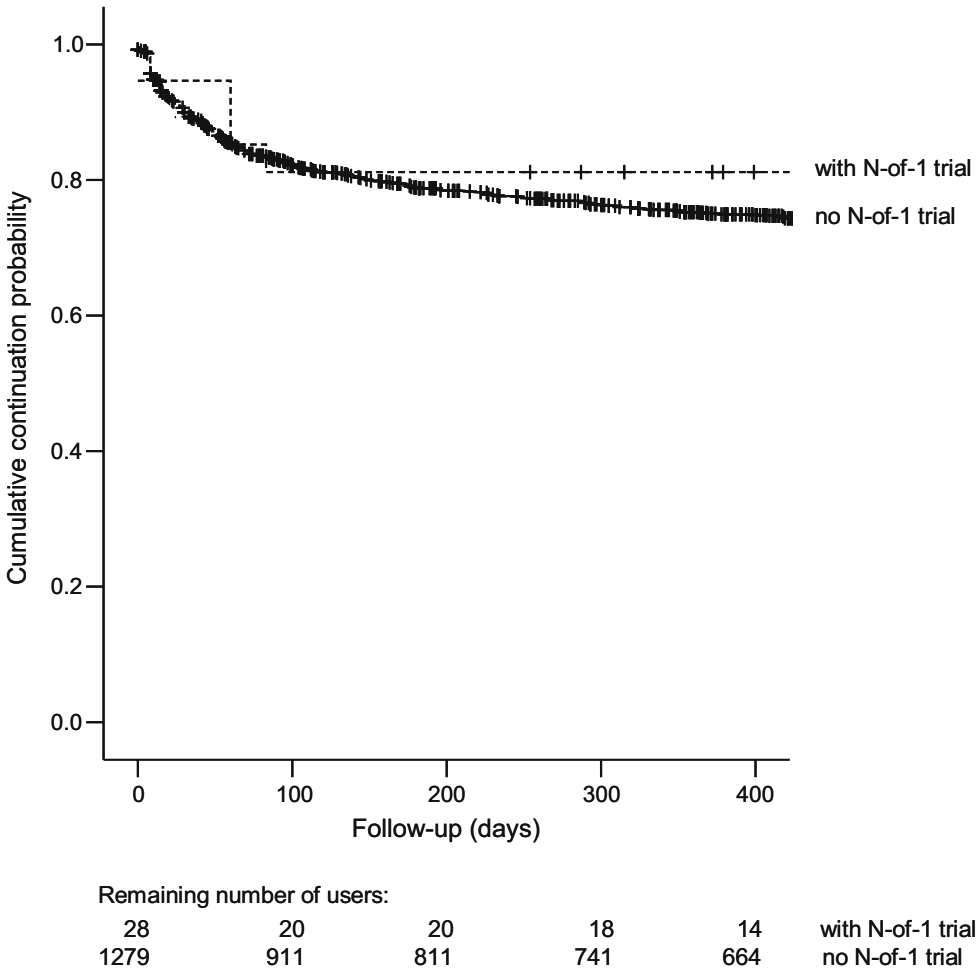

Fig. 1 Continuation of stimulant treatment in youths <20 years, who started stimulant treatment in 2000–2003 without an N-of-1 trial (n=1,279) and with an N-of-1 trial (n=28)

means of a statistical test. A study by Wallace and Koefoed showed that visual inspection resulted in a greater likelihood that treatments were falsely accepted as effective as is generally acceptable by a statistical inspection [26]. However, even if statistical tests were used, none of the N-of-1 protocols described by the physicians appeared to have had enough cycles of the same treatment to deliver a statistically significant result, which makes the evaluation of these N-of-1 trials of questionable value. At least three cycles of the same treatment are necessary to deliver a statistically significant result. Adjunct statistical evaluation of N-of-1 trials is possible though onerous for clinicians [4, 8, 20]. This lack of statistical resource indicates an opportunity for the development of an N-of-1 service such as has been available in other countries [9, 17]. Such a national N-of-1 service could assist individual physicians in performing and evaluating N-of-1 trials in a more appropriate way.

The database part of the study showed that the proportion of youths starting stimulant treatment with an N-of-1 trial ranged from 0.6 to 3.3% per year. No statistically significant difference could be detected between the continuation curves of stimulant treatment after starting with or without an N-of-1 trial. One would expect a steeper curve when N-of-1 trials were mainly used to discourage overenthusiastic prescribing [14]. Analogously, one would expect a less steep curve when N-of-1 trials were predominantly used to convince reluctant parents [11, 14]. However, the vast majority of the interviewed physicians in the current study did not mention these reasons for conducting an N-of-1 trial. The lack of a sound statistical evaluation of the N-of-1 trials may also explain why no difference was found between those who started with or without an N-of-1 trial, as non-responders and responders could not be distinguished accurately. Also, the number of youths starting stimulant treatment with an N-of-1 trial was probably too small to detect differences, if any. Two studies about the use of N-of-1 trials for the evaluation of existing treatment with quinine sulphate and non-steroidal anti-inflammatory drugs reported patients preferred to continue using these drugs, despite the fact that most patients did not clearly benefit from them [27, 28]. Therefore, when the aim of the N-of-1 trial is to identify the efficacy of an existing treatment, it is important to negotiate treatment continuation or cessation before starting the N-of-1 trial [12, 28].

The study presented has certain limitations that need to be taken into account. For the first part of the study, we used pharmacies as a starting point for our search for physicians performing N-of-1 trials with stimulants. Therefore, no estimations could be made about the proportion of child psychiatrists and paediatricians in the Netherlands actually using the N-of-1 methodology. There are two forms of 'non-response' in this study. Firstly, 50% of the pharmacists responded. Although this is not a high percentage, all regions were represented. Another reason concerning the inability to access physicians is that nine pharmacists were unable or unwilling to give names of physicians for us to interview. However, we think we covered most of the different aspects of N-of-1 trials procedures because no new information was obtained after the tenth interview.

To detect N-of-1 trials with stimulants in our database, inclusion criteria were formulated based on a consensus discussion with pharmacists, which in theory may have lead to an underestimation of the proportion of stimulant treatments starting with an N-of-1 trial. The chosen time frame of a maximum 2 weeks between dispension of compounded methylphenidate capsules and placebo capsules was chosen because none of the interviewed physicians used treatment periods longer than 2 weeks. To investigate the effect of this time frame we repeated the selection of N-of-1 trials using a time frame of 3 weeks. This increased time frame lead to inclusion of other compounded capsules with adjunct medication (e.g. melatonin, risperidon, olanzapin, lithium) and did not lead to the detection of any additional N-of-1 trials meeting the criteria.

An N-of-1 trial can be a useful tool in deciding whether a stimulant treatment is a suitable treatment for the individual patient [6, 11, 13, 14, 26]. Moreover, we think that a well-conducted N-of-1 trial is more ethically acceptable than the usual trial of therapy because an N-of-1 trial is a systematic double-blind and placebo-controlled evaluation. This is especially the case, as a significant proportion of the 20–30% non-responders are expected to experience adverse effects [2]. The advantage of an N-of-1 trial over the usual titration is that youth, parents and physicians are blinded, which enhances the objective rating of behaviour changes. Also, youth and parents are more actively involved in the decision-making process. It has been shown that parents were more satisfied with their child's treatment after participating in an N-of-1 trial than after a normal trial of therapy, although rates of compliance did not differ after a 6-week and 3-month follow-up [11]. We think the use of an N-of-1 trial before stimulant treatment should be encouraged in clinical practice. More uniformity in the protocols used would make it easier for physicians to encompass the N-of-1 methodology in their daily practice. More uniformity in N-of-1 protocols is also helpful in making ready-for-use statistical tests easily available to the physician.

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